NCT Number: NCT05906732

SAP

Title: A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects. Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome

Study Number: LQT-1213 061

Amendment of Cardiac Statistical Analysis Plan

Part 2

A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects.

Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome

Protocol: LQT-1213-0061

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Version: 2.0 (Amendment)
Date: 19 SEP 2024

VERSION 2.0
PREPARED BY:

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VERSION 1.0
PREPARED BY:

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REVIEWED BY:

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Date

1 Abbreviations

Abbreviation	Term/Description
AUC	Area under the curve
CI	Confidence interval
CRU	Clinical research unit
ECG	Electrocardiogram
HR	Heart rate
LQT2	Long QT Syndrome Type 2
LQT3	Long QT Syndrome Type 3
LQTS	Long QT syndrome
Min	Minimum
Max	Maximum
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	PR interval of the ECG
QRS	QRS interval of the ECG
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SGK-1	Serum and glucocorticoid- regulated kinase 1
TID	Three times a day

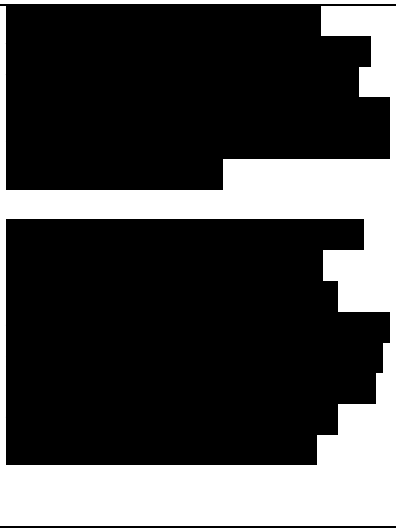
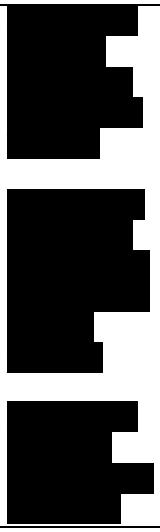
2 Introduction

[redacted]

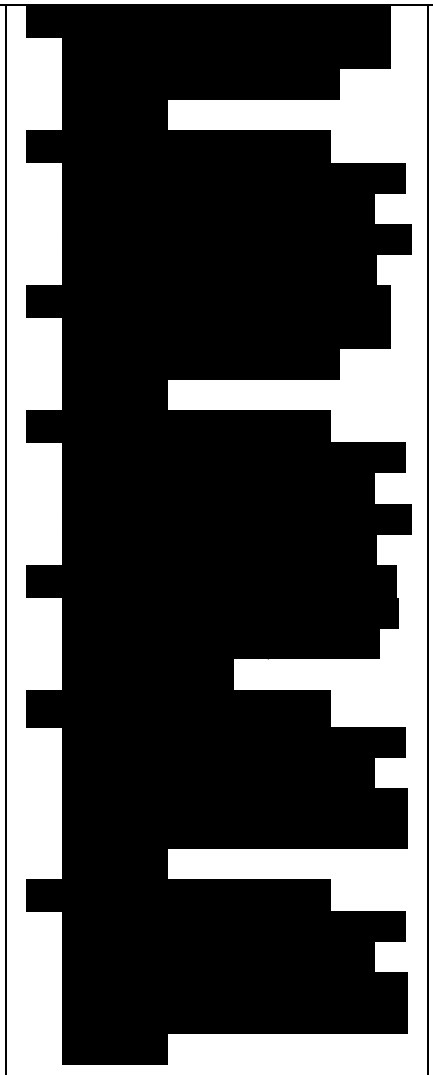
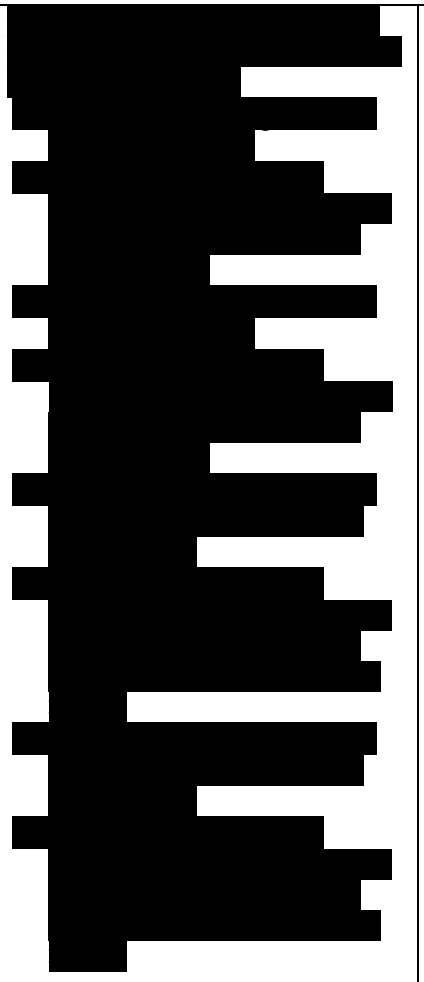
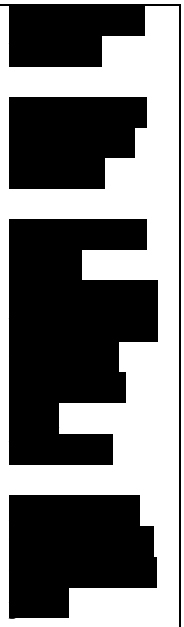
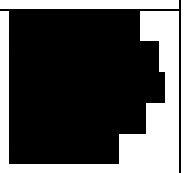
[redacted]

Section	Original Text	Amended Text	Rationale
3	This will be a Phase 2, single-blind, placebo run-in, multiple-dose safety study to evaluate the safety, tolerability, and PK of LQT-1213 in patients with LQT2 and LQT3. All patients will have a QTcF >490 and <600ms. Patients will be recruited by the sponsor using a network of cardiologists who treat LQTS patients and transported to the inpatient clinical research unit to participate in the study. After initial remote screening by the clinical research unit, individual patients will undergo a 2-day, single blind run-in period followed by dosing of LQT- 1213. Approximately 7 days after the end of treatment in Period 2, the Follow-up visit will be conducted remotely via telephone call. The duration of treatment for each subject in the study will be approximately 13 days, from admission on Day –2 to the telephone follow-up call. This	This will be a Phase 2a, single-blind, placebo run-in, multiple-dose safety study to evaluate the safety, tolerability, and PK of LQT-1213 in patients with LQT2 and LQT3. All patients will have a QTcF ≥480 and ≤560 ms. Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be enrolled. After initial remote screening by the clinical research unit (CRU), individual patients will undergo a 1-day, single blind run-in period followed by 3 dosing days of LQT-1213, administered three times a day (TID) at time 0, 8, and 16 hours on Days 2 and 3, with the final dose on Day 4 at time 0, though these time points may be adjusted based upon emerging data. Approximately 7 days after discharge from the CRU, the Follow-up visit will be conducted remotely via telephone call. The duration of treatment for each subject in the study will be approximately 13 days, from admission on Day -1 to the	Update per Protocol v7.0.

	does not include the 28-day screening period.	telephone follow-up call. This does not include the 60-day screening period.	
4	In Part 2, ECG data will be collected from Day -1 through Day 5. At each timepoint, three ECGs will be recorded and 3 beats analyzed per ECG. For analysis purpose, the average of all analyzed ECG complexes on the triplicate ECGs will be averaged in all ECG analyses. While 24-hour Holter were collected from which ECGs can be extracted, this analysis utilizes concomitantly recorded 12 lead ECGs. The timepoints for cardiodynamic ECG assessments can be found in Appendix 8 of the protocol.	In Part 2, ECG data will be collected from Day -1 through Day 5. At each time point, three (triplicate) ECGs will be recorded. For analysis purpose, the average of the triplicates ECGs will be analyzed. Additional post-hoc analyses based on all values of the triplicates were also conducted. While 24-hour Holter were collected from which ECGs can be extracted, this analysis utilizes concomitantly recorded 12 lead ECGs. The time points for cardiodynamic ECG assessments can be found in Appendix D of the protocol.	Update per Protocol v7.0.
5.1	None	New sentences were added: All ECG data will be summarized by LQT-1213 dose groups of 16 mg and 7 mg, unless otherwise specified. Typically, the confidence intervals (CIs) shall be rounded to two decimal places greater than the precision of the original value; however, due to space constraint on the printout, as well as for easier review, the CIs were rounded (post-hoc) to one decimal place greater than the precision of the original value.	Clarification on general approach for data summaries and analyses.
6.1	Each ECG parameter will be summarized by visit. All data will be listed, including each reading and the average of all readings for each timepoint. Descriptive statistics (e.g., number of subjects, mean, SD, median, maximum and minimum) will be used to summarize the absolute values of the ECG variables and the corresponding change- from-baseline values for all subjects at each time point on each of Days 1-5. Data-based (i.e., not model-based) 2-sided 90%, 85%,	Each ECG parameter will be summarized by visit [redacted] Descriptive statistics will be used to summarize the values of the ECG variables and the corresponding changes (and percent changes) from baseline values at each time point on each of Days 1-5. The 2-sided 90%, 85%, and 80% CIs of the means will be derived based on t-test.	Clarification on general approach for data summaries and by-subject listings.

	and 80% 2-sided CI of the mean will be summarized for the absolute and change-from-baseline data only.		
6.2	In this analysis, QTcF values at each timepoint on Day 2, 4, and 5 will be compared to the time-matched QTcF values on Day 1 (placebo) using paired t-test. 	In this analysis, QTcF values at each time point on Days 2 and 4 will be compared to the time-matched QTcF values on Day 1 (placebo) using paired t-test, which is the same as analyzing the difference of the time-matched QTcF values using one-sample t-test. 	Deletion of Day 5 as the time points are not the same as Day 1; Clarification on analysis methods and correction on multiple p-values; Addition of statistical interpretation on p-value versus multiple CIs; Addition of new post-hoc analyses that pooled 16 mg and 7 mg dose group together.
6.3			

	[redacted]	[redacted]	[redacted]
6.4	**Key Placebo-Corrected Analyses** • The QTcF values on Days 2, 4 and 5 during the following times, will be compared to the values on Day 1 (placebo) utilizing the trapezoidal methodology (AUC). o Hours 2-6 o Hours 0-8 o Hours 0-12	**Key Placebo-corrected Analyses** • The QTcF values collected on Days 2 and 4 during the following time intervals will be compared to the values on Day 1 (placebo) utilizing the trapezoidal methodology for area under the curve (AUC) calculation. Furthermore, the average AUC, which is defined as the AUC divided by the actual time span of the AUC time interval within each subject, were analyzed as post-hoc analyses. An additional time interval from hours 3 to 6 was added after examining the time course of the QTcF data. o Hours 2-6 o Hours 0-8 o Hours 0-12 o Hours 3-6	Deletion of Day 5 as the time points are not the same as Day 1; Clarification on analysis methods using AUC; Addition of new post-hoc analyses using average AUC; Addition of new post-hoc analyses using time interval of Hours 3-6.
6.4	[redacted]	[redacted]	[redacted]
6.4	[redacted]	[redacted]	[redacted]

			
6.4	None		

		[redacted]	
6.5	[redacted]	[redacted]	[redacted]

3 Study Design

The study is a Phase 1b/2a two-part (Part 1 and Part 2) trial in male and female subjects between 19 and 60 years of age (inclusive). Part 1 is a randomized, double-blind, crossover, dose escalation, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of SGK-1 kinase inhibition by LQT-1213 on dofetilide-induced corrected QT (QTc) prolongation in healthy adult subjects. Part 2 is a single-blind, multiple-dose escalation safety study to evaluate the safety, tolerability, and PK of LQT-1213 in patients diagnosed with Long QT Syndrome

Type 2 (LQT2) and Long QT Syndrome Type 3 (LQT3).

Part 1

The design of Part 1 can be found in the protocol. The statistical plan for Part 1 was described in a separate statistical analysis plan.

Part 2

This will be a Phase 2a, single-blind, placebo run-in, multiple-dose safety study to evaluate the safety, tolerability, and PK of LQT-1213 in patients with LQT2 and LQT3. All patients will have a QTcF ≥480 and ≤560 ms. Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be enrolled.

After initial remote screening by the clinical research unit (CRU), individual patients will undergo a 1-day, single blind run-in period followed by 3 dosing days of LQT-1213, administered three times a day (TID) at time 0, 8, and 16 hours on Days 2 and 3, with the final dose on Day 4 at time 0, though these time points may be adjusted based upon emerging data.

Approximately 7 days after discharge from the CRU, the Follow-up visit will be conducted remotely via telephone call. The duration of treatment for each subject in the study will be approximately 13 days, from admission on Day -1 to the telephone follow-up call. This does not include the 60-day screening period.

4 Cardiodynamic ECG Assessment

[redacted]

4.1 Cardiodynamic ECG Objectives and Endpoints

The objectives of the study are to:

1) Evaluate the effect of up to two separate oral doses of LQT-1213 on QTcF prolongation in patients with LQT2 and LQT3 using the QTc interval corrected for heart rate by the Fridericia's formula (QTcF).

[redacted]

5 Statistical Methods

5.1 General Methodology

For continuous variables the following descriptive statistics will be provided: number of subjects, mean, standard error of the mean (SE), standard deviation (SD), minimum (min), maximum (max), and median. For categorical variables, descriptive statistics will include the number and percentage of subjects in each category, using either the number of subjects in the treatment group or the number of subjects with non-missing values as the denominator for the percentages. All ECG data will be summarized by LQT-1213 dose groups of 16 mg and 7 mg, unless otherwise specified. Min and max values will be rounded to the precision of the original value. Means and medians will be rounded to one decimal place greater than the precision of the original value. SDs and SEs will be rounded to two decimal places greater than the precision of the original value. Typically, the confidence intervals (CIs) shall be rounded to two decimal places greater than the precision of the original value; however, due to space constraint on the printout, as well as for easier review, the CIs were rounded (post-hoc) to one decimal place greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place. P-values will be presented with four decimal places and values less than 0.0001 will be presented as <0.0001. All inferential statistical testing will be two-sided, and log-transformation of values may be performed when applicable.

In the case where a safety laboratory variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for summary. In listings, these data will be presented as recorded with the sign.

By-subject listings, including data at scheduled and unscheduled visits, will be sorted by treatment group, subject number, study visit and time point.

5.2 Baseline

[redacted]

6 Analysis

6.1 Summary Statistics Analysis

Each ECG parameter will be summarized by visit. The average of the triplicates at each time point will be presented in listings. Descriptive statistics will be used to summarize the values of the ECG variables and the corresponding changes (and percent changes) from baseline values at each time point on each of Days 1-5. The 2-sided 90%, 85%, and 80% CIs of the means will be derived based on t-test.

6.2 Time-based Placebo-corrected Analysis

In this analysis, QTcF values at each time point on Days 2 and 4 will be compared to the time-matched QTcF values on Day 1 (placebo) using paired t-test, which is the same as analyzing the difference of the time-matched QTcF values using one-sample t-test.

[redacted] The mean difference, median, SD, min, max, 2-sided 90%, 85%, and 80% CIs, and p-value will be reported. The null hypothesis will be rejected at significance levels of 0.1, 0.15, or 0.2 if the p-value is less than 0.1, 0.15, or 0.2, corresponding to 2-sided 90%, 85%, and 80% CIs, respectively.

Additional post-hoc analyses were conducted for all time-matched placebo-corrected analyses by pooling subjects in the LQT-1213 16 mg and 7 mg dose groups together.

The same analyses will be conducted on HR, PR and QRS.

[redacted]

6.4 Additional Key Analysis

Key Placebo-corrected Analyses

- The QTcF values collected on Days 2 and 4 during the following time intervals, will be compared to the values on Day 1 (placebo) utilizing the trapezoidal methodology for area under the curve (AUC) calculation. Furthermore, the average AUC, which is defined as the AUC divided by the actual time span of the AUC time interval within each subject, were analyzed as post-hoc analyses. An additional time interval from hours 3 to 6 was added after examining the time course of the QTcF data.

    - Hours 2-6
    - Hours 0-8
    - Hours 0-12
    - Hours 3-6

Key Time-based Analyses

[redacted]

Subgroup Analyses

QTcF analyses specified in Section 6.2 and 6.3 will be repeated for the following cohorts:

[redacted]

- Subjects with a Day 1 predose baseline QTc ≥500 ms, if there are at least 2 subjects

[redacted]

[redacted]